

EXHIBIT A

(PART 1 OF 4)



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Say et al.

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(54) **ANALYTE MONITORING DEVICE AND METHODS OF USE**

4,098,574 7/1978 Dappen .
4,100,048 7/1978 Pompei et al. .

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(21) Appl. No.: **09/070,677**(22) Filed: **Apr. 30, 1998**(51) **Int. Cl.⁷** **A61B 5/05**(52) **U.S. Cl.** **600/345**; 600/365; 128/903(58) **Field of Search** 600/300-301, 600/346, 306-309, 345-365, 372, 385-390; 604/174-180; 128/897-898, 903, 904, 920(56) **References Cited**

U.S. PATENT DOCUMENTS

Re. 32,947	6/1989	Dormer et al. .
3,260,656	7/1966	Ross, Jr. .
3,653,841	4/1972	Klein .
3,719,564	3/1973	Lilly, Jr. et al. .
3,776,832	12/1973	Oswin et al. .
3,837,339	9/1974	Aisenberg et al. .
3,926,760	12/1975	Allen et al. .
3,972,320	8/1976	Kalman .
3,979,274	9/1976	Newman .
4,008,717	2/1977	Kowarski .
4,016,866	4/1977	Lawton .
4,055,175	10/1977	Clemens et al. .
4,059,406	11/1977	Fleet .
4,076,596	2/1978	Connery et al. .

227 029 A3 9/1985 (DD) .
29 03 216 8/1979 (DE) .

(List continued on next page.)

OTHER PUBLICATIONS

Abruna, H. D. et al., "Rectifying Interfaces Using Two-Layer, Films of Electrochemically Polymerized Vinylpyridine and Vinylbipyrine Complexes of Ruthenium and Iron on Electrodes," *J. Am. Chem. Soc.*, 103(1):1-5 (Jan. 14, 1981).

(List continued on next page.)

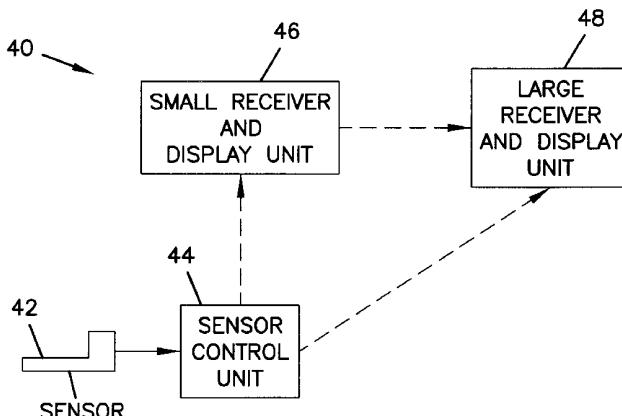
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(57) **ABSTRACT**

An analyte monitor includes a sensor, a sensor control unit, and a display unit. The sensor has, for example, a substrate, a recessed channel formed in the substrate, and conductive material disposed in the recessed channel to form a working electrode. The sensor control unit typically has a housing adapted for placement on skin and is adapted to receive a portion of an electrochemical sensor. The sensor control unit also includes two or more conductive contacts disposed on the housing and configured for coupling to two or more contact pads on the sensor. A transmitter is disposed in the housing and coupled to the plurality of conductive contacts for transmitting data obtained using the sensor. The display unit has a receiver for receiving data transmitted by the transmitter of the sensor control unit and a display coupled to the receiver for displaying an indication of a level of an analyte. The analyte monitor may also be part of a drug delivery system to alter the level of the analyte based on the data obtained using the sensor.

94 Claims, 26 Drawing Sheets

US 6,175,752 B1

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U.S. PATENT DOCUMENTS

4,151,845	5/1979	Clemens .	4,781,798	11/1988	Gough .
4,168,205	9/1979	Danninger et al. .	4,784,736	11/1988	Lonsdale et al. .
4,172,770	10/1979	Semersky et al. .	4,795,707	1/1989	Niiyama et al. .
4,178,916	12/1979	McNamara .	4,796,634	1/1989	Huntsman et al. .
4,206,755	6/1980	Klein .	4,805,624	2/1989	Yao et al. .
4,224,125	9/1980	Nakamura et al. .	4,813,424	3/1989	Wilkins .
4,240,438	12/1980	Updike et al. .	4,815,469	3/1989	Cohen et al. .
4,247,297	1/1981	Berti et al. .	4,820,399	4/1989	Senda et al. .
4,340,458	7/1982	Lerner et al. .	4,822,337	4/1989	Newhouse et al. .
4,352,960	10/1982	Dormer et al. .	4,830,959	5/1989	McNeil et al. .
4,356,074	10/1982	Johnson .	4,832,797	5/1989	Vadgama et al. .
4,365,637	12/1982	Johnson .	4,840,893	6/1989	Hill et al. .
4,366,033	12/1982	Richter et al. .	4,848,351	7/1989	Finch .
4,375,399	3/1983	Havas et al. .	4,871,351	10/1989	Feingold .
4,384,586	5/1983	Christiansen .	4,871,440	10/1989	Nagata et al. .
4,390,621	6/1983	Bauer .	4,874,500	10/1989	Madou et al. .
4,401,122	8/1983	Clark, Jr. .	4,890,620	1/1990	Gough .
4,404,066	9/1983	Johnson .	4,894,137	1/1990	Takizawa et al. .
4,418,148	11/1983	Oberhardt .	4,897,162	1/1990	Lewandowski et al. .
4,427,770	1/1984	Chen et al. .	4,897,173	1/1990	Nankai et al. .
4,431,004	2/1984	Bessman et al. .	4,909,908	3/1990	Ross et al. .
4,436,094	3/1984	Cerami .	4,911,794	3/1990	Parce et al. .
4,440,175	4/1984	Wilkins .	4,917,800	4/1990	Lonsdale et al. .
4,450,842	5/1984	Zick et al. .	4,919,141	4/1990	Zier et al. .
4,458,686	7/1984	Clark, Jr. .	4,919,767	4/1990	Vadgama et al. .
4,461,691	7/1984	Frank .	4,923,586	5/1990	Katayama et al. .
4,469,110	9/1984	Slarna .	4,927,516	5/1990	Yamaguchi et al. .
4,477,314	10/1984	Richter et al. .	4,934,369	6/1990	Maxwell .
4,484,987	11/1984	Gough .	4,935,105	6/1990	Takizawa et al. .
4,522,690	6/1985	Venkatesetty .	4,935,345	6/1990	Churchouse .
4,524,114	6/1985	Samuels et al. .	4,938,860	7/1990	Guilbeau et al. .
4,526,661	7/1985	Steckhan et al. .	4,944,299	7/1990	Wogoman .
4,534,356	8/1985	Papadakis .	4,950,378	8/1990	Silvian .
4,538,616	9/1985	Rogoff .	4,953,552 *	9/1990	Nagara .
4,543,955	10/1985	Schrooppel .	4,954,129	9/1990	DeMarzo
4,545,382	10/1985	Higgins et al. .	4,969,468	11/1990	600/300
4,552,840	11/1985	Riffer .	4,970,145	11/1990	Giuliani et al. .
4,560,534	12/1985	Kung et al. .	4,974,929	12/1990	Byers et al. .
4,571,292	2/1986	Liu et al. .	4,986,271	1/1991	Bennetto et al. .
4,573,994	3/1986	Fischell et al. .	4,994,167	2/1991	Curry .
4,581,336	4/1986	Malloy et al. .	5,001,054	3/1991	Wilkins .
4,595,011	6/1986	Phillips .	5,050,612	9/1991	Shults et al. .
4,619,754	10/1986	Niki et al. .	5,058,592	10/1991	Churchouse .
4,627,445	12/1986	Garcia et al. .	5,070,535	12/1991	Matsumura .
4,627,908	12/1986	Miller .	5,082,550	1/1992	Wagner .
4,633,878	1/1987	Bombardieri .	5,082,786	1/1992	Rishpon et al. .
4,637,403	1/1987	Garcia et al. .	5,089,112	2/1992	Nakamoto .
4,650,547	3/1987	Gough .	5,095,904	3/1992	Skotheim et al. .
4,654,197	3/1987	Lilja et al. .	5,101,814	4/1992	Seligman et al. .
4,655,880	4/1987	Liu .	5,108,564	4/1992	Palti .
4,655,885	4/1987	Hill et al. .	5,109,850	5/1992	Szuminsky et al. .
4,671,288	6/1987	Gough .	5,120,420	6/1992	Blanco et al. .
4,679,562	7/1987	Luksha .	5,126,034	6/1992	Nankai et al. .
4,680,268	7/1987	Clark, Jr. .	5,133,856	7/1992	Carter et al. .
4,682,602	7/1987	Prohaska .	5,135,003	8/1992	Wang et al. .
4,684,537	8/1987	Graetzel et al. .	5,141,868	8/1992	Shanks et al. .
4,685,463	8/1987	Williams .	5,161,532	11/1992	Joseph .
4,703,756	11/1987	Gough et al. .	5,165,407	11/1992	Wilson et al. .
4,711,245	12/1987	Higgins et al. .	5,174,291	12/1992	Shutlts et al. .
4,717,673	1/1988	Wrighton et al. .	5,190,041	3/1993	Schoonen et al. .
4,721,601	1/1988	Wrighton et al. .	5,192,416	3/1993	Palti .
4,721,677	1/1988	Clark, Jr. .	5,198,367	3/1993	Wang et al. .
4,726,378	2/1988	Kaplan .	5,202,261	4/1993	Aizawa et al. .
4,726,716	2/1988	McGuire .	5,205,920	4/1993	Musho et al. .
4,757,022	7/1988	Shults et al. .	5,208,154	4/1993	Oyama et al. .
4,758,323	7/1988	Davis et al. .	5,209,229	5/1993	Weaver et al. .
4,759,371	7/1988	Frantzki .	5,217,595	5/1993	Gill .
4,759,828	7/1988	Young et al. .	5,229,282	6/1993	Smith et al. .
4,764,416	8/1988	Ueyama et al. .	5,250,439	7/1993	Yoshioka et al. .
4,776,944	10/1988	Janata et al. .	5,262,035	10/1993	Musho et al. .
			5,262,305	11/1993	Gregg et al. .
				11/1993	Heller et al. .

US 6,175,752 B1

Page 3

5,264,103	11/1993	Yoshioka et al. .	5,954,685	*	9/1999	Tierny	600/386
5,264,104	11/1993	Gregg et al. .	5,971,922	*	10/1999	Arita et al.	600/365
5,264,106	11/1993	McAleer et al. .					
5,271,815	12/1993	Wong .					
5,279,294	1/1994	Anderson et al. .	3934299		10/1990	(DE) .	
5,286,362	2/1994	Hoenes et al. .	0 010 375 A1		4/1980	(EP) .	
5,286,364	2/1994	Yacynych et al. .	0 026 995 A1		4/1981	(EP) .	
5,288,636	2/1994	Pollmann et al. .	0 048 090 A2		3/1982	(EP) .	
5,293,546	3/1994	Tadros et al. .	0 078 636 A1		5/1983	(EP) .	
5,320,098	6/1994	Davidson .	0 096 228 A1		12/1983	(EP) .	
5,320,725	6/1994	Gregg et al. .	0 125 139 A2		11/1984	(EP) .	
5,322,063 *	6/1994	Allen et al.	600/372		0 127 958 A2	12/1984 (EP) .	
5,337,747	8/1994	Nefelt .			0 136 362 A1	4/1985 (EP) .	
5,352,348	10/1994	Young et al. .			0 170 375 A2	2/1986 (EP) .	
5,356,348	10/1994	Young et al. .			0 177 743 A2	4/1986 (EP) .	
5,356,786	10/1994	Heller et al. .			0 080 304 B1	5/1986 (EP) .	
5,368,028	11/1994	Palti .			0 184 909 A2	6/1986 (EP) .	
5,372,133	12/1994	Hogen Esch .			0 206 218 A2	12/1986 (EP) .	
5,376,251	12/1994	Kaneko et al. .			0 230 472 A1	8/1987 (EP) .	
5,378,628	1/1995	Gratzel et al. .			0 241 309 A3	10/1987 (EP) .	
5,387,327	2/1995	Khan .			0 245 073 A2	11/1987 (EP) .	
5,390,671	2/1995	Lord et al. .			0 278 647 A2	8/1988 (EP) .	
5,391,250	2/1995	Cheney, II et al. .			0 359 831 A1	3/1990 (EP) .	
5,395,504	3/1995	Saurer et al. .			0 368 290 A1	10/1990 (EP) .	
5,400,782 *	3/1995	Beaubiah	600/309		390 390 A1	10/1990 (EP) .	
5,411,647	5/1995	Johnson et al. .			0 400 918 A1	12/1990 (EP) .	
5,437,999	8/1995	Diebold et al. .			0 453 283 A1	10/1991 (EP) .	
5,469,846	11/1995	Khan .			0 470 290 A1	2/1992 (EP) .	
5,491,474 *	2/1996	Suni et al.	128/903		0 127 958 B2	3/1992 (EP) .	
5,494,562	2/1996	Maley et al. .			0 255 291 B1	6/1992 (EP) .	
5,496,453	3/1996	Uenoyama et al. .			1394171	5/1975 (GB) .	
5,497,772	3/1996	Schulman et al. .			1599241	9/1981 (GB) .	
5,531,878	7/1996	Vadgama et al. .			2 073 891	10/1981 (GB) .	
5,545,191	8/1996	Mann et al. .			2 154 003	2/1988 (GB) .	
5,560,357	10/1996	Faupel et al. .			2 204 408	11/1988 (GB) .	
5,562,713 *	10/1996	Silvian	128/903		2 254 436	10/1992 (GB) .	
5,565,085	10/1996	Ikeda et al. .			54-41191	4/1979 (JP) .	
5,567,302	10/1996	Song et al. .			55-10581	1/1980 (JP) .	
5,568,806	10/1996	Cheney, II et al. .			55-10583	1/1980 (JP) .	
5,569,186	10/1996	Lord et al. .			55-10584	1/1980 (JP) .	
5,582,184	12/1996	Erickson et al. .			55-12406	1/1980 (JP) .	
5,582,697	12/1996	Ikeda et al. .			56-163447	12/1981 (JP) .	
5,582,698	12/1996	Flaherty et al. .			57-70448	4/1982 (JP) .	
5,586,553	12/1996	Halili et al. .			60-173457	9/1985 (JP) .	
5,589,326	12/1996	Deng et al. .			60-173458	9/1985 (JP) .	
5,593,852	1/1997	Heller et al. .			60-173459	9/1985 (JP) .	
5,596,150	1/1997	Arndt et al. .			61-90050	5/1986 (JP) .	
5,617,851	4/1997	Lipkovker .			62-85855	4/1987 (JP) .	
5,628,890	5/1997	Carter et al. .			62-114747	5/1987 (JP) .	
5,651,869	7/1997	Yoshioka et al. .			63-58149	3/1988 (JP) .	
5,660,163	8/1997	Schulman et al. .			63-128252	5/1988 (JP) .	
5,670,031	9/1997	Hintsche et al. .			63-139246	6/1988 (JP) .	
5,680,858	10/1997	Hansen et al. .			63-294799	12/1988 (JP) .	
5,682,233	10/1997	Brinda .			63-317757	12/1988 (JP) .	
5,695,623	12/1997	Michel et al. .			63-317758	12/1988 (JP) .	
5,708,247	1/1998	McAleer et al. .			1-114746	5/1989 (JP) .	
5,711,297 *	1/1998	Iliff et al.	600/300		1-114747	5/1989 (JP) .	
5,711,861 *	1/1998	Ward et al.	600/365		1-124060	5/1989 (JP) .	
5,711,862	1/1998	Sakoda et al. .			1-134244	5/1989 (JP) .	
5,741,211	4/1998	Renirie et al. .			1-156658	6/1989 (JP) .	
5,771,001 *	6/1998	Cobb	128/903		2-62958	3/1990 (JP) .	
5,791,344 *	8/1998	Schulman et al.	600/300		2-120655	5/1990 (JP) .	
5,800,420 *	9/1998	Gross et al.	604/890.1		2-287145	11/1990 (JP) .	
5,807,375	9/1998	Gross et al. .			2-310457	12/1990 (JP) .	
5,820,551 *	10/1998	Hill et al.	600/365		3-26956	2/1991 (JP) .	
5,820,622 *	10/1998	Gross et al.	604/890.1		3-28752	2/1991 (JP) .	
5,822,715	10/1998	Worthington et al. .			3-202764	9/1991 (JP) .	
5,827,184 *	10/1998	Netherly et al.	600/385		5-72171	3/1993 (JP) .	
5,840,020	11/1998	Heinonen et al. .			5-196595	8/1993 (JP) .	
5,842,983 *	12/1998	Abel et al.	600/372		6-190050	7/1994 (JP) .	
5,885,211 *	3/1999	Eppstein et al.	600/365		7-55757	3/1995 (JP) .	

US 6,175,752 B1

Page 4

7-72585	3/1995	(JP).
8-285814	11/1996	(JP).
8-285815	11/1996	(JP).
9-21778	1/1997	(JP).
9-101280	4/1997	(JP).
9-285459	11/1997	(JP).
10-170471	6/1998	(JP).
1281988 A1	1/1987	(SU).
WO 89/05119	11/1985	(WO).
WO 89/08713	9/1989	(WO).
WO 90/05300	5/1990	(WO).
WO 90/05910	5/1990	(WO).
WO 91/01680	2/1991	(WO).
WO 91/04704	4/1991	(WO).
WO 91/15993	10/1991	(WO).
WO 92/13271	8/1992	(WO).
WO 94/20602	9/1994	(WO).
WO 94/27140	11/1994	(WO).
WO 96/30431	10/1996	(WO).
WO 96/35370	11/1996	(WO).
WO 97/02847	1/1997	(WO).
WO 97/19344	5/1997	(WO).
WO 97/42882	11/1997	(WO).
WO 97/42883	11/1997	(WO).
WO 97/42886	11/1997	(WO).
WO 97/42888	11/1997	(WO).
WO 97/43962	11/1997	(WO).

OTHER PUBLICATIONS

Albery, W. J. et al., "Amperometric enzyme electrodes. Part II. Conducting salts as electrode materials for the oxidation of glucose oxidase," *J. Electroanal. Chem. Interfacial Electrochem.*, 194(2) (1 page—Abstract only) (1985).

Albery, W. J. et al., "Amperometric Enzyme Electrodes," *Phil. Trans. R Soc. Lond. B* 316:107–119 (1987).

Alcock, S. J. et al., "Continuous Analyte Monitoring to Aid Clinical Practice," *IEEE Engineering in Medicine and Biology*, 319–325 (1994).

Anderson, L. B. et al., "Thin-Layer Electrochemistry: Steady-State Methods of Studying Rate Processes," *J. Electroanal. Chem.*, 10:295–395 (1965).

Bartlett, P. N. et al., "Covalent Binding of Electron Relays to Glucose Oxidation," *J. Chem. Soc. Chem. Commun.*, 1603–1604 (1987).

Bartlett, P. N. et al., "Modification of glucose oxidase by tetrathiafulvalene," *J. Chem. Soc., Chem. Commun.*, 16 (1 page—Abstract only) (1990).

Bartlett, P. N. et al., "Strategies for the Development of Amperometric Enzyme Electrodes," *Biosensors*, 3:359–379 (1987/88).

Bindra, D.S. et al., "Design and in Vitro Studies of a Needle-Type Glucose Sensor for Subcutaneous Monitoring," *Anal. Chem.*, 63(17):1692–1696 (Sep. 1, 1991).

Bobbioni-Harsch, E. et al., "Lifespan of subcutaneous glucose sensors and their performances during dynamic glycaemia changes in rats," *J. Biomed. Eng.* 15:457–463 (1993).

Brandt J. et al., "Covalent attachment of proteins to polysaccharide carriers by means of benzoquinone," *Biochim. Biophys. Acta*, 386(1) (1 page Abstract only) (1975).

Brownlee, M. et al., "A Glucose-Controlled Insulin-Delivery System: Semisynthetic Insulin Bound to Lectin," *Science*, 206(4423):1190–1191 (Dec. 7, 1979).

Cass, A.E.G. et al., "Ferricinium Ion As An Electron Acceptor for Oxido-Reductases," *J. Electroanal. Chem.*, 190:117–127 (1985).

Cass, A.E.G. et al., "Ferrocene-Mediated Enzyme Electrode for Amperometric Determination of Glucose", *Anal. Chem.*, 56(4):667–671 (Apr. 1984).

Castner, J. F. et al., "Mass Transport and Reaction Kinetic Parameters Determined Electrochemically for Immobilized Glucose Oxidase," *Biochemistry*, 23(10):2203–2210 (1984).

Claremont, D.J. et al., "Biosensors for Continuous In Vivo Glucose Monitoring", *IEEE Engineering in Medicine and Biology Society 10th Annual International Conference*, New Orleans, Louisiana, 3 pgs. (Nov. 4–7, 1988).

Clark L.C. et al., "Differential Anodic Enzyme Polarography for the Measurement of Glucose", *Oxygen Transport to Tissue: Instrumentation, Methods, and Physiology*, 127–132 (1973).

Clark, L.C., Jr. et al., "Electrode Systems for Continuous Monitoring in Cardiovascular Surgery," *Annals New York Academy of Sciences*, pp. 29–45 (1962).

Clark, L.C. et al., "Long-term Stability of Electroenzymatic Glucose Sensors Implanted in Mice," *Trans. Am. Soc. Artif. Intern. Organs*, XXXIV:259–265 (1988).

Clarke, W. L., et al., "Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose," *Diabetes Care*, 10(5):622–628 (Sep.–Oct. 1987).

Csöregi, E. et al., "Design, Characterization, and One-Point in Vivo Calibration of a Subcutaneously Implanted Glucose Electrode," *Anal. Chem.* 66(19):3131–3138 (Oct. 1, 1994).

Csöregi, E. et al., "Design and Optimization of a Selective Subcutaneously Implantable Glucose Electrode Based on "Wired" Glucose Oxidase," *Anal. Chem.* 67(7):1240–1244 (Apr. 1, 1995).

Csöregi, E. et al., "On-Line Glucose Monitoring by Using Microdialysis Sampling and Amperometric Detection Based on "Wired" Glucose Oxidase in Carbon Paste," *Mikrochim. Acta*, 121:31–40 (1995).

Davis, G., "Electrochemical Techniques for the Development of Amperometric Biosensors", *Biosensors*, 1:161–178 (1985).

Degani, Y. et al., "Direct Electrical Communication between Chemically Modified Enzymes and Metal Electrodes. 1. Electron Transfer from Glucose Oxidase to Metal Electrodes via Electron Relays, Bound Covalently to the Enzyme," *J. Phys. Chem.* 91(6):1285–1289 (1987).

Degani, Y. et al., "Direct Electrical Communication between Chemically Modified Enzymes and Metal Electrodes. 2. Methods for Bonding Electron-Transfer Relays to Glucose Oxidase and D-Amino-Acid Oxidase," *J. Am. Chem. Soc.*, 110(8):2615–2620 (1988).

Degani, Y. et al., "Electrical Communication between Redox Centers of Glucose Oxidase and Electrodes via Electrostatically and Covalently Bound Redox Polymers," *J. Am. Chem. Soc.*, 111:2357–2358 (1989).

Denisevich, P. et al., "Unidirectional Current Flow and Charge State Trapping at Redox Polymer Interfaces on Bilayer Electrodes: Principles, Experimental Demonstration, and Theory," *J. Am. Chem. Soc.*, 103(16):4727–4737 (1981).

Dicks, J. M., "Ferrocene modified polypyrrole with immobilised glucose oxidase and its application in amperometric glucose microbiosensors," *Ann. Biol. clin.*, 47:607–619 (1989).

Engstrom, R.C., "Electrochemical Pretreatment of Glassy Carbon Electrodes", *Anal. Chem.*, 54(13):2310–2314 (Nov. 1982).

US 6,175,752 B1

Page 5

Engstrom, R.C. et al., "Characterization of Electrochemically Pretreated Glassy Carbon Electrodes", *Anal. Chem.*, 56(2):136–141 (Feb. 1984).

Ellis, C. D., "Selectivity and Directed Charge Transfer through an Electroactive Metallocopolymer Film," *J. Am. Chem. Soc.*, 103(25):7480–7483 (1981).

Feldman, B.J. et al., "Electron Transfer Kinetics at Redox Polymer/Solution Interfaces Using Microelectrodes and Twin Electrode Thin Layer Cells", *J. Electroanal. Chem.*, 194(1):63–81 (Oct. 10, 1985).

Fischer, H. et al., "Intramolecular Electron Transfer Mediated by 4,4'-Bipyridine and Related Bridging Groups", *J. Am. Chem. Soc.*, 98(18):5512–5517 (Sep. 1, 1976).

Foulds, N.C. et al., "Enzyme Entrapment in Electrically Conducting Polymers," *J. Chem. Soc., Faraday Trans 1*, 82:1259–1264 (1986).

Foulds, N.C. et al., "Immobilization of Glucose Oxidase in Ferrocene–Modified Pyrrole Polymers," *Anal. Chem.*, 60(22):2473–2478 (Nov. 15, 1988).

Frew, J.E. et al., "Electron–Transfer Biosensors", *Phil. Trans. R Soc. Lond.*, B316:95–106 (1987).

Gorton, L. et al., "Selective detection in flow analysis based on the combination of immobilized enzymes and chemically modified electrodes," *Analytica Chimica Acta*, 250:203–248 (1991).

Gregg, B. A. et al., "Cross–Linked Redox Gels Containing Glucose Oxidase for Amperometric Biosensor Applications," *Analytical Chemistry*, 62(3):258–263 (Feb. 1, 1990).

Gregg, B. A. et al., "Redox Polymer Films Containing Enzymes. 1. A Redox–Conducting Epoxy Cement: Synthesis, Characterization, and Electrocatalytic Oxidation of Hydroquinone," *J. Phys. Chem.*, 95(15):5970–5975 (1991).

Hale, P D et al., "A New Class of Amperometric Biosensor Incorporating a Polymeric Electron–Transfer Mediator," *J. Am. Chem. Soc.*, 111(9):3482–3484 (1989).

Harrison, D.J. et al., "Characterization of Perfluorosulfonic Acid Polymer Coated Enzyme Electrodes and a Miniaturized Integrated Potentiostat for Glucose Analysis in Whole Blood", *Anal. Chem.*, 60(19):2002–2007 (Oct. 1, 1988).

Hawkridge, F. M. et al., "Indirect Coulometric Titration of Biological Electron Transport Components," *Analytical Chemistry*, 45(7):1021–1027 (Jun. 1973).

Heller, A., "Amperometric biosensors based on three–dimensional hydrogel–forming epoxy networks," *Sensors and Actuators B*, 13–14:180–183 (1993).

Heller, A., "Electrical Connection of Enzyme Redox Centers to Electrodes," *J. Phys. Chem.*, 96(9):3579–3587 (1992).

Heller, A., "Electrical Wiring of Redox Enzymes," *Acc. Chem. Res.*, 23(5):129–134 (1990).

Ianniello, R.M. et al. "Immobilized Enzyme Chemically Modified Electrode as an Amperometric Sensor", *Anal. Chem.*, 53(13):2090–2095 (Nov. 1981).

Ianniello, R.M. et al., "Differential Pulse Voltammetric Study of Direct Electron Transfer in Glucose Oxidase Chemically Modified Graphite Electrodes", *Anal. Chem.*, 54(7):1098–1101 (Jun. 1981).

Ikeda, T. et al., "Glucose oxidase–immobilized benzoquinone–carbon paste electrode as a glucose sensor," *Agric. Biol. Chem.*, 49(2) (1 page—Abstract only) (1985).

Ikeda, T. et al., "Kinetics of Outer–Sphere Electron Transfers Between Metal Complexes in Solutions and Polymeric Films on Modified Electrodes", *J. Am. Chem. Soc.*, 103(25):7422–7425 (Dec. 16, 1981).

Johnson, J. M. et al., "Potential–Dependent Enzymatic Activity in an Enzyme Thin–Layer Cell," *Anal. Chem.*, 54:1377–1383 (1982).

Johnson, K. W., "Reproducible Electrodeposition of Biomolecules for the Fabrication of Miniature Electroenzymatic Biosensors", *Sensors and Actuators B Chemical*, B5:85–89 (1991).

Jonsson, G. et al., "An Amperometric Glucose Sensor Made by Modification of a Graphite Electrode Surface With Immobilized Glucose Oxidase and Adsorbed Mediator", *Biosensors*, 1:355–368 (1985).

Josowicz, M. et al., "Electrochemical Pretreatment of Thin Film Platinum Electrodes", *J. Electrochem. Soc.*, 135(1):112–115 (Jan. 1988).

Katakis, I. et al., "Electrostatic Control of the Electron Transfer Enabling Binding of Recombinant Glucose Oxidase and Redox Polyelectrolytes," *J. Am. Chem. Soc.*, 116(8):3617–3618 (1994).

Katakis, I. et al., "L–α–Glycerophosphate and L–Lactate Electrodes Based on the Electrochemical ‘Wiring’ of Oxidases," *Analytical Chemistry*, 64(9):1008–1013 (May 1, 1992).

Kenausis, G. et al., "Wiring of glucose oxidase and lactate oxidase within a hydrogel made with poly(vinyl pyridine) complexed with [Os(4,4'-dimethoxy–2,2'-bipyridine)₂C1]⁺²⁺," *J. Chem. Soc., Faraday Trans.*, 90(20):4131–4136 (1996).

Koudelka, M. et al., "In–Vivo Behaviour of Hypodermically Implanted Microfabricated Glucose Sensors", *Biosensors & Bioelectronics*, 6(1):31–36 (1991).

Kulys, J. et al., "Mediatorless peroxidase electrode and preparation of bienzyme sensors," *Bioelectrochemistry and Bioenergetics*, 24:305–311 (1990).

Lager, W. et al., "Implantable Electrocatalytic Glucose Sensor," *Horm. Metab. Res.*, 26:526–530 (Nov. 1994).

Lindner, E. et al. "Flexible (Kapton–Based) Microsensor Arrays of High Stability for Cardiovascular Applications", *J. Chem. Soc, Faraday Trans.*, 89(2):361–367 (Jan. 21, 1993).

Maidan, R. et al., "Elimination of Electrooxidizable Interferant–Produced Currents in Amperometric Biosensors," *Analytical Chemistry*, 64(23):2889–2896 (Dec. 1, 1992).

Mastrototaro, J.J. et al., "An Electroenzymatic Glucose Sensor Fabricated on a Flexible Substrate", *Sensors and Biosensors B Chemical*, B5:139–144 (1991).

McNeil, C. J. et al., "Thermostable Reduced Nicotinamide Adenine Dinucleotide Oxidase: Application to Amperometric Enzyme Assay," *Anal. Chem.*, 61(1):25–29 (Jan. 1, 1989).

Miyawaki, O. et al., "Electrochemical and Glucose Oxidase Coenzyme Activity of Flavin Adenine Dinucleotide Covalently Attached to Glassy Carbon at the Adenine Amino Group", *Biochimica et Biophysica Acta*, 838:60–68 (1985).

Moatti–Sirat, D. et al., "Evaluating in vitro and in vivo the interference of ascorbate and acetaminophen on glucose detection by a needle–type glucose sensor," *Biosensors & Bioelectronics*, 7(5):345–352 (1992).

Moatti–Sirat, D. et al., "Reduction of acetaminophen interference in glucose sensors by a composite Nafion membrane: demonstration in rats and man," *Diabetologia*, 37(6) (1 page—Abstract only) (Jun. 1994).

Moatti–Sirat, D. et al., "Towards continuous glucose monitoring: in vivo evaluation of a miniaturized glucose sensor implanted for several days in rat subcutaneous tissue," *Diabetologia*, 35(3) (1 page—Abstract only) (Mar. 1992).

US 6,175,752 B1

Page 6

Nagy, G. et al., "A New Type of Enzyme Electrode: The Ascorbic Acid Eliminator Electrode," *Life Sciences*, 31(23):2611–2616 (1982).

Nakamura, S. et al., "Effect of Periodate Oxidation on the Structure and Properties of Glucose Oxidase," *Biochimica et Biophysica Acta.*, 445:294–308 (1976).

Narazimhan, K. et al., "p-Benzoquinone activation of metal oxide electrodes for attachment of enzymes," *Enzyme Microb. Technol.*, 7(6) (1 page—Abstract only) (1985).

Ohara, T. J. et al., "Glucose Electrodes Based on Cross-Linked $[\text{Os}(\text{bpy})_2\text{Cl}]^{+2+}$ Complexed Poly(1-vinylimidazole) Films," *Analytical Chemistry*, 65(23):3512–3516 (Dec. 1, 1993).

Ohara, T. J., "Osmium Bipyridyl Redox Polymers Used in Enzyme Electrodes," *Platinum Metals Rev.*, 39(2):54–62 (Apr. 1995).

Ohara, T. J. et al., "'Wired' Enzyme Electrodes for Amperometric Determination of Glucose or Lactate in the Presence of Interfering Substances," *Analytical Chemistry*, 66(15):2451–2457 (Aug. 1, 1994).

Olivier, C. N. et al., "In vivo Measurement of Carbon Dioxide Tension with a Miniature Electrode," *Pflugers Arch.* 373:269–272 (1978).

Paddock, R. et al., "Electrocatalytic reduction of hydrogen peroxide via direct electron transfer from pyrolytic graphite electrodes to irreversibly adsorbed cytochrome c peroxidase," *J. Electroanal. Chem.*, 260:487–494 (1989).

Palleschi, G. et al., "A Study of Interferences in Glucose Measurements in Blood by Hydrogen Peroxide Based Glucose Probes," *Anal. Biochem.*, 159:114–121 (1986).

Pankramov, I. et al., "Sol-gel derived renewable-surface biosensors," *Journal of Electroanalytical Chemistry*, 393:35–41 (1995).

Pathak, C. P. et al., "Rapid Photopolymerization of Immunoprotective Gels in Contact with Cells and Tissue," *J. Am. Chem. Soc.*, 114(21):8311–8312 (1992).

Pickup, J., "Developing glucose sensors for in vivo use," *Tibtech*, 11:285–289 (Jul. 1993).

Pickup, J. C. et al., "In vivo molecular sensing in diabetes mellitus: an implantable glucose sensor with direct electron transfer," *Diabetologia*, 32(3):213–217 (1989).

Pickup, J. et al., "Potentially-implantable, amperometric glucose sensors with mediated electron transfer: improving the operating stability," *Biosensors*, 4(2) (1 page—Abstract only) (1989).

Pishko, M.V. et al., "Amperometric Glucose Microelectrodes Prepared Through Immobilization of Glucose Oxidase in Redox Hydrogels," *Anal. Chem.*, 63(20):2268–2272 (Oct. 15, 1991).

Poitout, V. et al., "A glucose monitoring system for on line estimation in man of blood glucose concentration using a miniaturized glucose sensor implanted in the subcutaneous tissue and a wearable control unit," *Diabetologia*, 36(7) (1 page—Abstract only) (Jul. 1993).

Poitout, V. et al., "Calibration in dogs of a subcutaneous miniaturized glucose sensor using a glucose meter for blood glucose determination," *Biosensors & Bioelectronics*, 7:587–592 (1992).

Poitout, V. et al., "In vitro and in vivo evaluation in dogs of a miniaturized glucose sensor," *ASAIO Transactions*, 37(3) (1 page—Abstract only) (Jul.–Sep. 1991).

Pollak, A. et al., "Enzyme immobilization by Condensation Copolymerization into Cross-Linked Polyacrylamide Gels," *J. Am. Chem. Soc.*, 102(20):6324–6336 (1980).

Reach, G. et al., "Can Continuous Glucose Monitoring Be Used for the Treatment of Diabetes?" *Analytical Chemistry*, 64(6):381–386 (Mar. 15, 1992).

Rebrin, K. et al., "Automated Feedback Control of subcutaneous Glucose Concentration in Diabetic Dogs", *Diabetologia*, 32(8):573–576 (Aug. 1989).

Sakakida, M. et al., "Ferrocene-mediate needle-type glucose sensor covered with newly designed biocompatible membrane," *Sensors and Actuators B*, 13–14:319–322 (1993).

Samuels, G. J. et al., "An Electrode-Supported Oxidation Catalyst Based on Ruthenium (IV). pH "Encapsulation" in a Polymer Film," *J. Am. Chem. Soc.*, 103(2):307–312 (1981).

Sasso, S.V. et al., "Electropolymerized 1,2-Diaminobenzene as a Means to Prevent Interferences and Fouling and to Stabilize Immobilized Enzyme in Electrochemical Biosensors", *Anal. Chem.*, 62(11):1111–1117 (Jun. 1, 1990).

Scheller, F. et al., "Enzyme electrodes and their application," *Phil. Trans. R Soc. Lond.*, B 316:85–94 (1987).

Schmehl, R.H. et al., "The Effect of Redox Site Concentration on the Rate of Mediated Oxidation of Solution Substrates by a Redox Copolymer Film", *J. Electroanal. Chem.*, 152:97–109 (Aug. 25, 1983).

Shichiri, M. et al., "Glycaemic Control in Pancrearectomized Dogs with a Wearable Artificial Endocrine Pancreas", *Diabetologia*, 24(3):179–184 (Mar. 1983).

Sirtampalam, G. et al., "Surface-Modified Electrochemical Detector for Liquid Chromatography", *Anal. Chem.*, 55(9):1608–1610 (Aug. 1983).

Soegijoko, S. et al., *Horm. Metab. Res., Suppl. Ser.* 12 (1 page—Abstract only) (1982).

Sprules, S. D. et al., "Evaluation of a New Disposable Screen-Printed Sensor Strip for the Measurement of NADH and Its Modification to Produce a Lactate Biosensor Employing Microliter Volumes," *Electroanalysis*, 8(6):539–543 (1996).

Sternberg, F. et al., "Calibration Problems of Subcutaneous Glucosensors when Applied "In-Situ" in Man," *Horm. metabl. Res.* 26:524–525 (1994).

Sternberg, R. et al., "Covalent Enzyme Coupling on Cellulose Acetate Membranes for Glucose Sensor Development," *Analytical Chemistry*, 60(24):2781–2786 (Dec. 15, 1988).

Sternberg, R. et al., "Study and Development of Multilayer Needle-type Enzyme-based Glucose Microsensors," *Biosensors*, 4:27–40 (1988).

Suckane, M., "Immobilization of glucose isomerase," *Zeitschrift fur Allgemeine Mikrobiologie*, 22(8):565–576 (1982).

Tajima, S. et al., "Simultaneous Determination of Glucose and 1,5-Anydroglucitol", *Chemical Abstracts*, 111(25):394 111:228556g (Dec. 18, 1989).

Tarashevich, M.R. "Bioelectrocatalysis", *Comprehensive Treatise of Electrochemistry*, 10 (Ch. 4):231–295 (1985).

Tatsuma, T. et al., "Enzyme Monolayer- and Bilayer-Modified Tin Oxide Electrodes for the Determination of Hydrogen Peroxide and Glucose," *Anal. Chem.*, 61(21):2352–2355 (Nov. 1, 1989).

Taylor, C. et al., "'Wiring' of glucose oxidase within a hydrogel made with polyvinyl imidazole complexed with $[\text{Os}-4,4'-\text{dimethoxy-2,2'-bipyridine}\text{Cl}]^{+2+}$," *Journal of Electroanalytical Chemistry*, 396:511–515 (1995).

US 6,175,752 B1

Page 7

Trojanowicz, M. et al., "Enzyme Entrapped Polypyrrole Modified Electrode for Flow-Injection Determination of Glucose," *Biosensors & Bioelectronics*, 5:149–156 (1990).

Turner, A.P.F. et al., "Diabetes Mellitus: Biosensors for Research and Management", *Biosensors*, 1:85–115 (1985).

Turner, R.F.B. et al., "A Biocompatible Enzyme Electrode for Continuous in vivo Glucose Monitoring in Whole Blood," *Sensors and Actuators*, B1(1–6):561–564 (Jan. 1990).

Tuzhi, P. et al., "Constant Potential Pretreatment of Carbon Fiber Electrodes for In vivo Electrochemistry", *Analytical Letters*, 24(6):935–945 (1991).

Umaha, M., "Protein-Modified Electrochemically Active Biomaterial Surface," *U.S. Army Research Office Report*, (12 pages) (Dec. 1988).

Urban, G. et al., "Miniaturized Thin-Film Biosensors Using Covalently Immobilized Glucose Oxidase", *Biosensors & Bioelectronics*, 6(7):555–562 (1991).

Velho, G. et al., "In Vitro and In Vivo Stability of Electrode Potentials in Needle-Type Glucose Sensors", *Diabetes*, 38(2):164–171 (Feb. 1989).

Velho, G. et al., "Strategies for calibrating a subcutaneous glucose sensor," *Biomed. Biochim. Acta*, 48(11/12):957–964 (1989).

Von Woedtke, T. et al., "In Situ Calibration of Implanted Electrochemical Glucose Sensors," *Biomed. Biochim. Acta*, 48(11/12):943–952 (1989).

Vrecke, M. S. et al., "Chapter 15: Hydrogen Peroxide Electrodes Based on Electrical Connection of Redox Centers of Various Peroxidases to Electrodes through a Three-Dimensional Electron-Relaying Polymer Network," *Diagnostic Biosensor Polymers*, 7 pgs. (Jul. 26, 1993).

Vrecke, M. et al., "Hydrogen Peroxide and β -Nicotinamide Adenine Dinucleotide Sensing Amperometric Electrodes Based on Electrical Connection of Horseradish Peroxidase Redox Centers to Electrodes through a Three-Dimensional Electron Relaying Polymer Network," *Analytical Chemistry*, 64(24):3084–3090 (Dec. 15, 1992).

Wang, J. et al., "Activation of Glassy Carbon Electrodes by Alternating Current Electrochemical Treatment", *Analytica Chimica Acta*, 167:325–334 (Jan. 1985).

Wang, J. et al., "Amperometric biosensing of organic peroxides with peroxidase-modified electrodes," *Analytica Chimica Acta*, 254:81–88 (1991).

Wang, D. L. et al., "Miniaturized Flexible Amperometric Lactate Probe," *Analytical Chemistry*, 65(8):1069–1073 (Apr. 15, 1993).

Wang, J. et al., "Screen-Printable Sol-Gel Enzyme-Containing Carbon Inks," *Analytical Chemistry*, 68(15):2705–2708 (Aug. 1, 1996).

Wang, J. et al., "Sol-Gel-Derived Metal-Dispersed Carbon Composite Amperometric Biosensors," *Electroanalysis*, 9(1):52–55 (1997).

Williams, D.L. et al., "Electrochemical-Enzymatic Analysis of Blood Glucose and Lactate", *Anal. Chem.*, 42(1):118–121 (Jan. 1970).

Wilson, G. S. et al., "Progress toward the Development of an Implantable Sensor for Glucose," *Clinical Chemistry*, 38(9):1613–1617 (1992).

Yabuki, S. et al., "Electro-conductive Enzyme Membrane," *J. Chem. Soc. Commun.*, 945–946 (1989).

Yang, I. et al., "Determination of Oxidase Enzyme Substrates Using Cross-Flow Thin-Layer Amperometry," *Electroanalysis*, 8(8–9):716–721 (1996).

Yao, S.J. et al., "The Interference of Ascorbate and Urea in Low-Potential Electrochemical Glucose Sensing", *Proceedings of the Twelfth Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 12(2):487–489 (Nov. 1–4, 1990).

Yao, T. et al., "A Chemically-Modified Enzyme Membrane Electrode As An Amperometric Glucose Sensor," *Analytica Chimica Acta*, 148:27–33 (1983).

Ye, L. et al., "High Current Density "Wired" Quinoprotein Glucose Dehydrogenase Electrode," *Anal. Chem.*, 65(3):238–241 (Feb. 1, 1993).

Yildiz, A. et al., "Evaluation of an Improved Thin-Layer Electrode," *Analytical Chemistry*, 40(70):1018–1024 (Jun. 1968).

Zamzow, K. et al., New Wearable Continuous Blood Glucose Monitor (BGM) and Artificial Pancreas (AP), *Diabetes*, 39:5A(20) (May 1990).

Zhang, Y. et al., "Application of cell culture toxicity tests to the development of implantable biosensors," *Biosensors & Bioelectronics*, 6:653–661 (1991).

Zhang, Y. et al., "Elimination of the Acetaminophen Interference in an Implantable Glucose Sensor," *Anal. Chem.*, 66:1183–1188 (1994).

* cited by examiner

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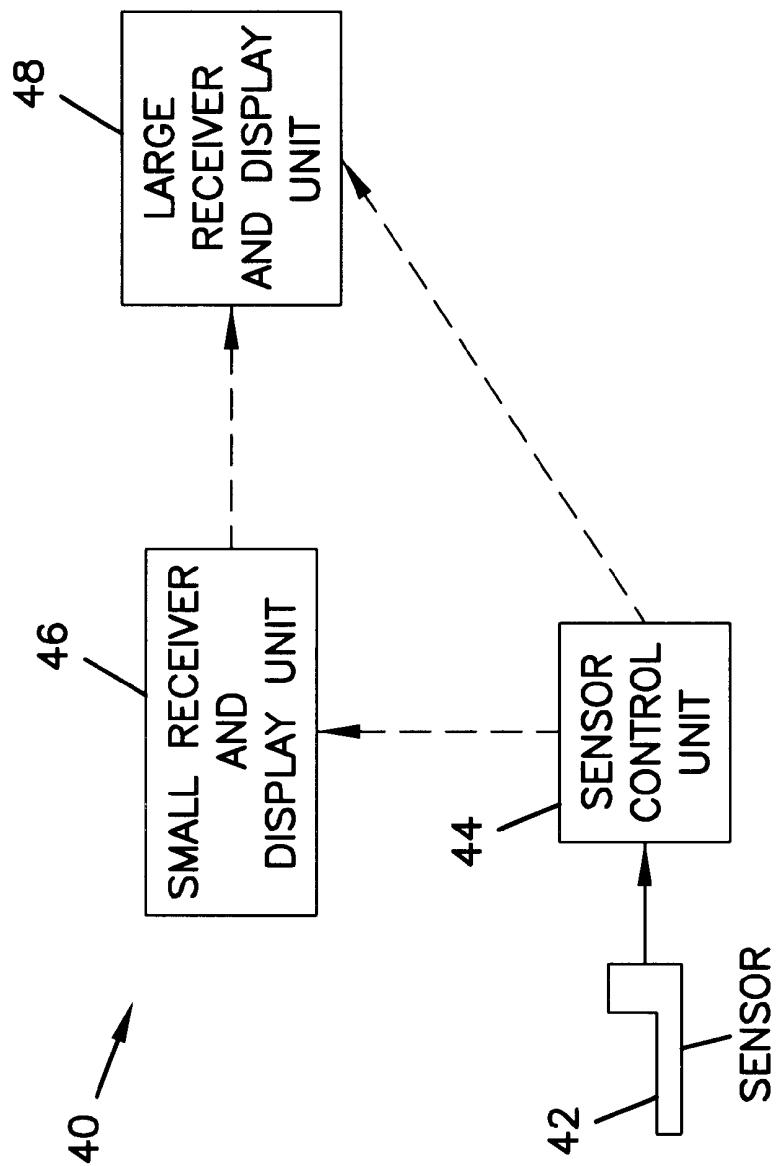


FIG. 1

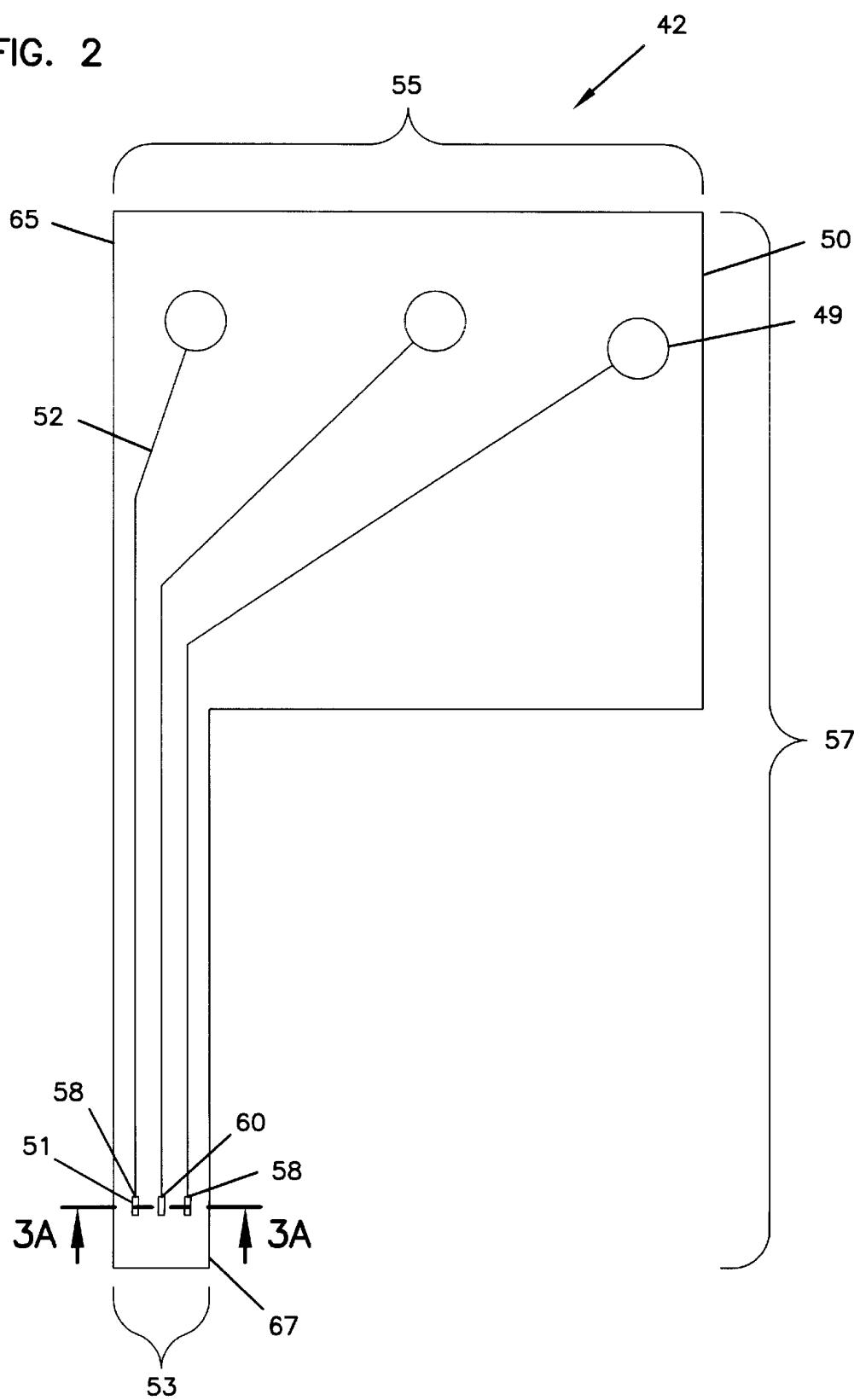
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FIG. 2



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FIG. 3A

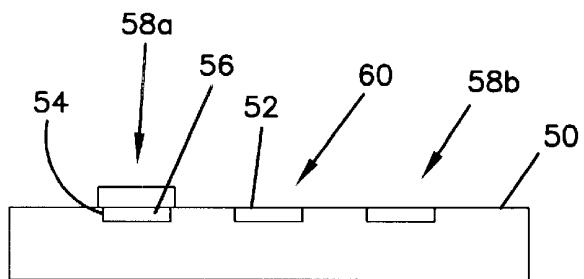


FIG. 3B

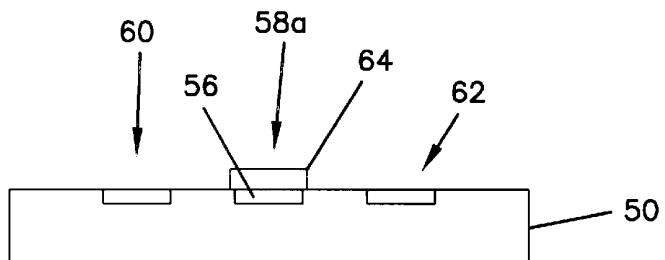


FIG. 9

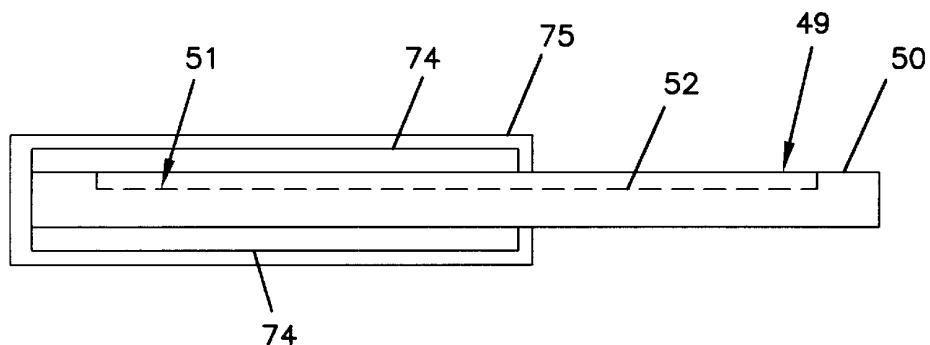
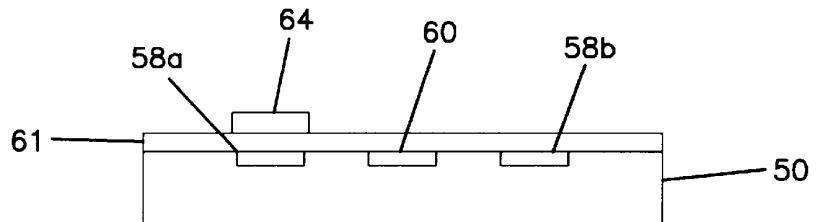


FIG. 4A



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FIG. 4B

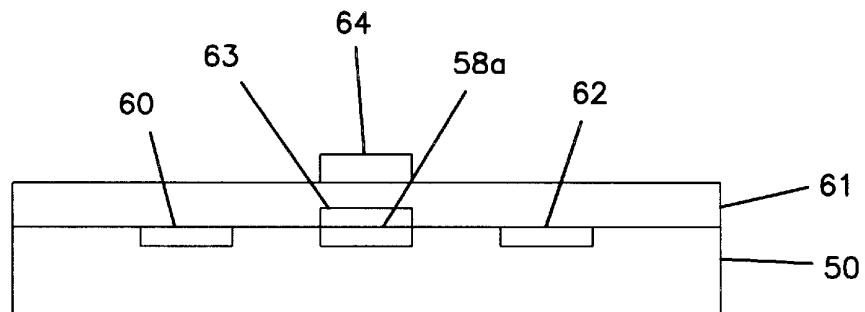
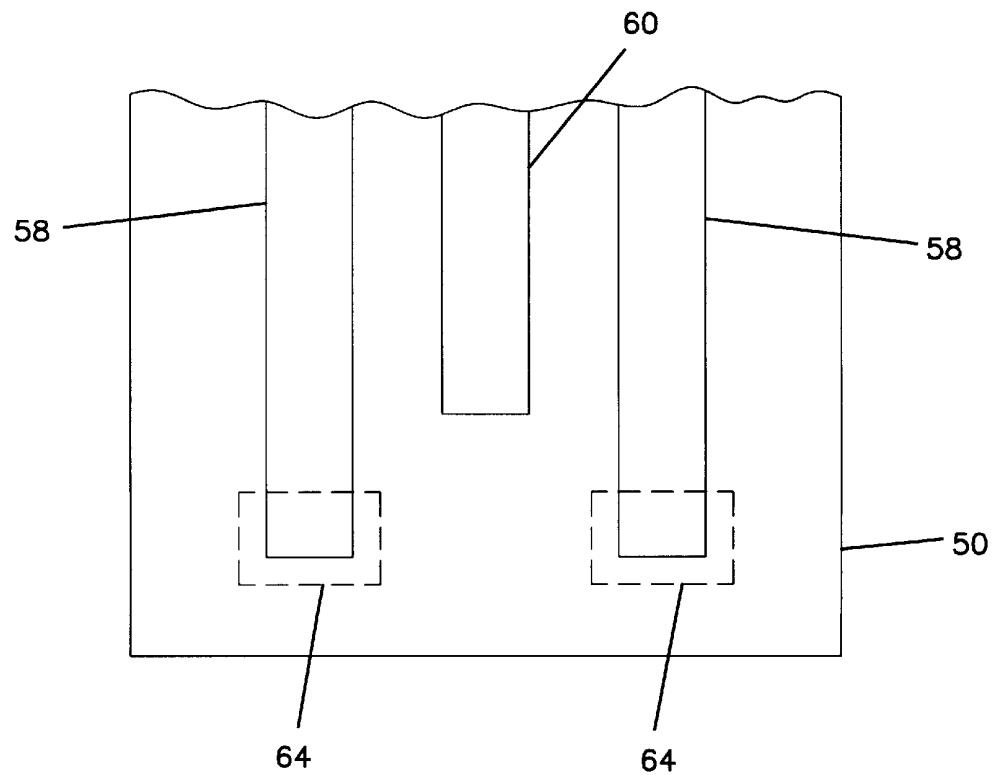


FIG. 5



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FIG. 6

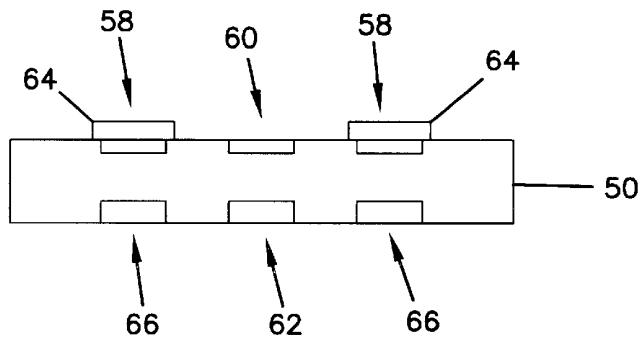


FIG. 7

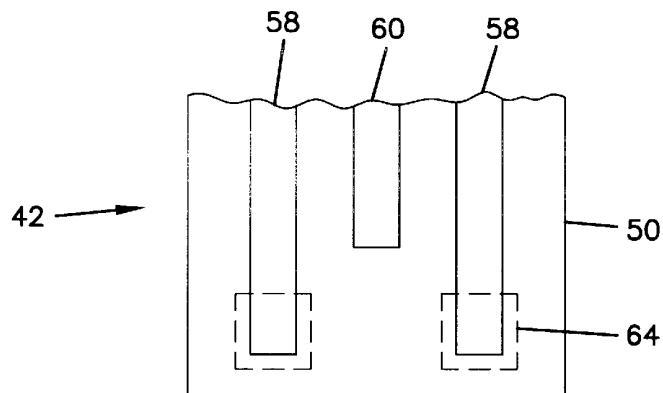
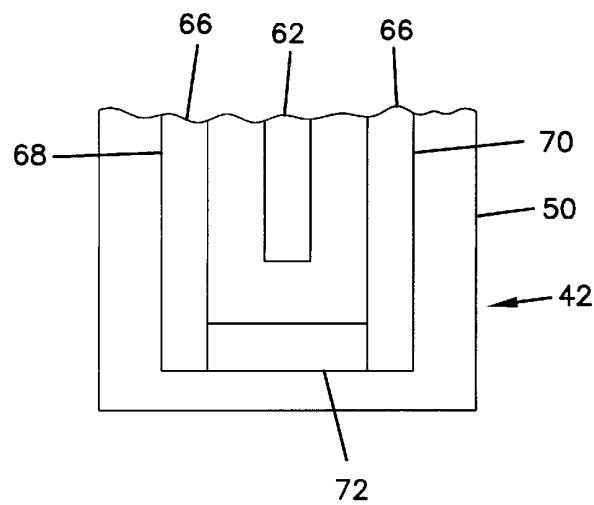


FIG. 8



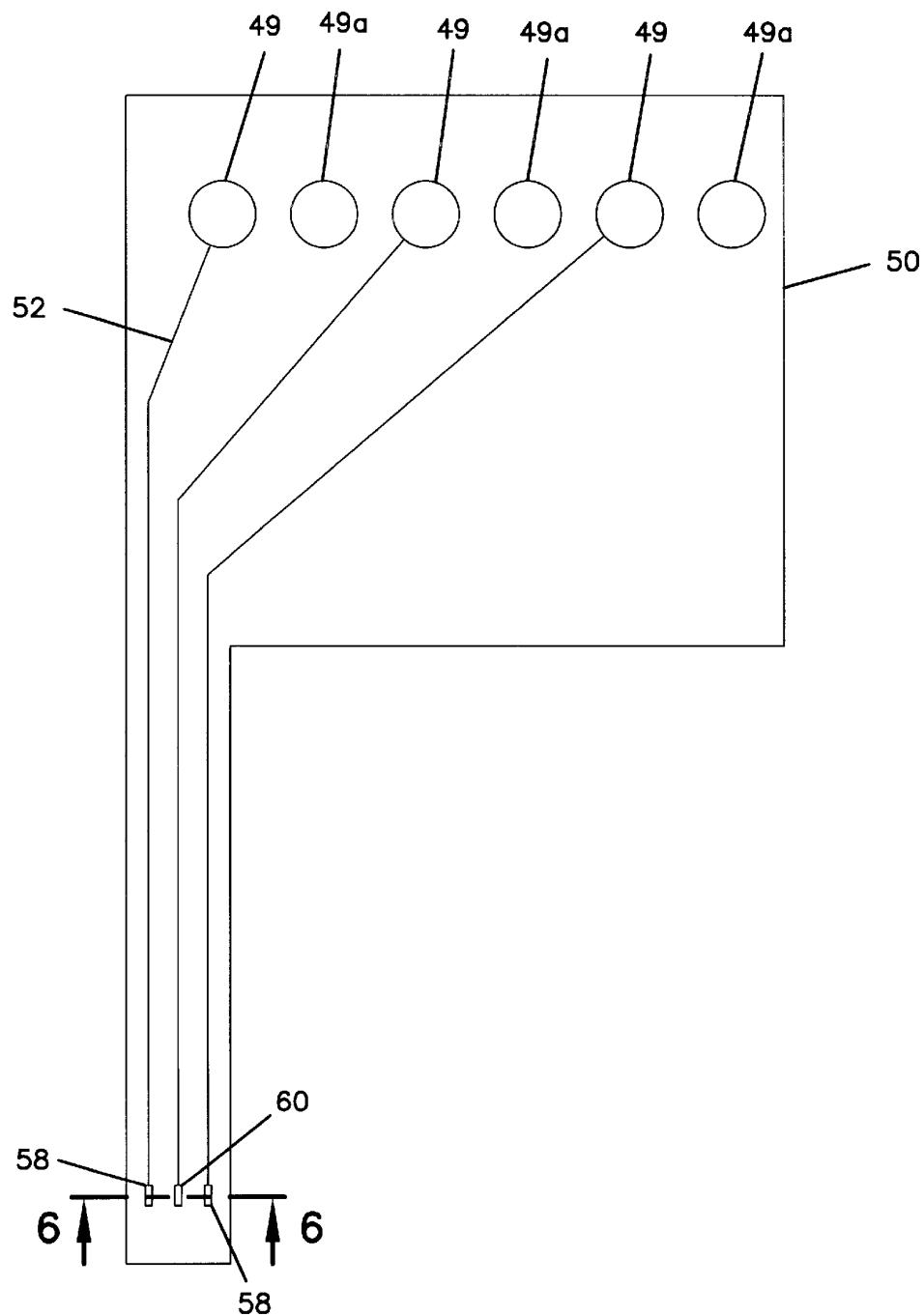
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FIG. 10



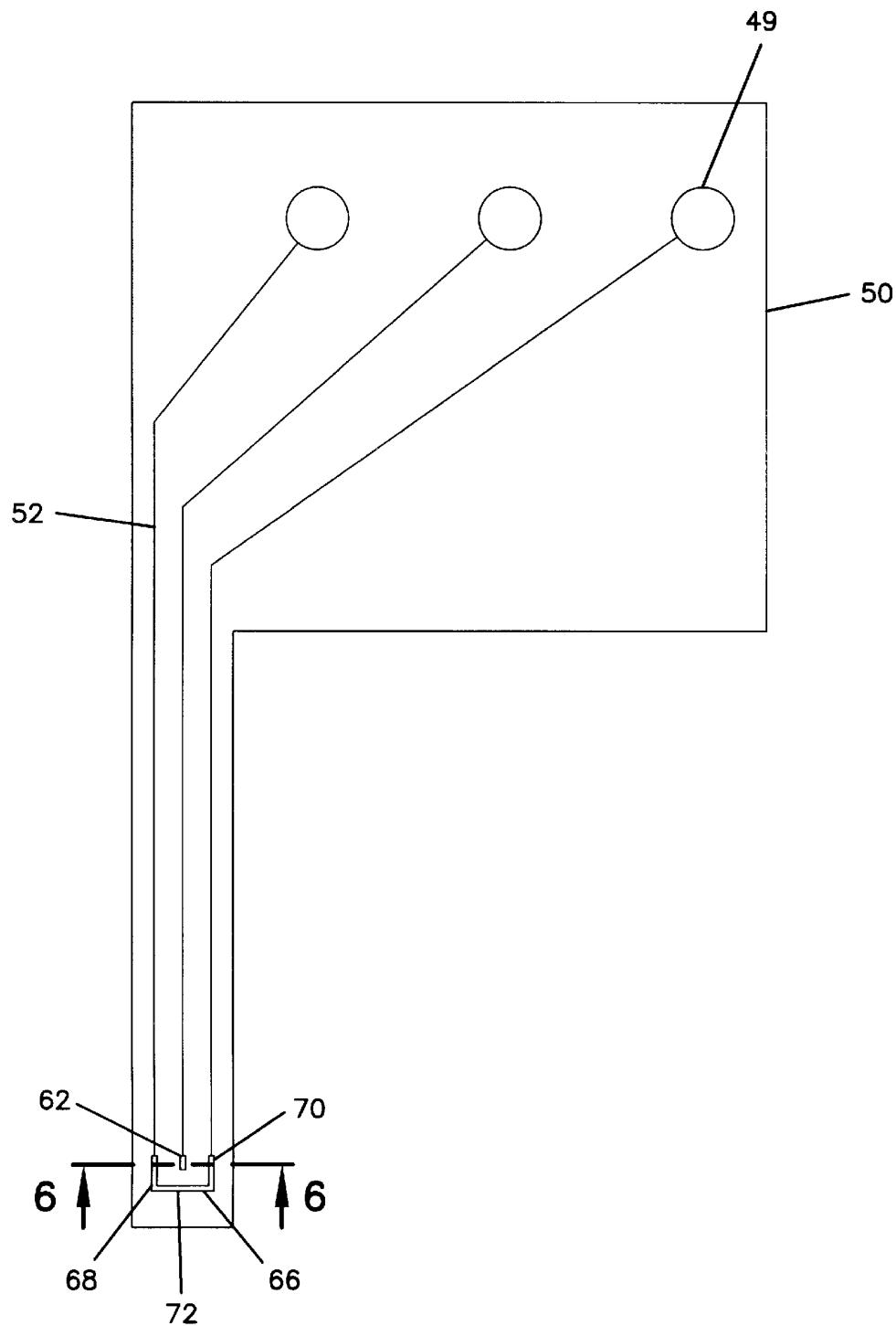
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FIG. 11



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FIG. 12

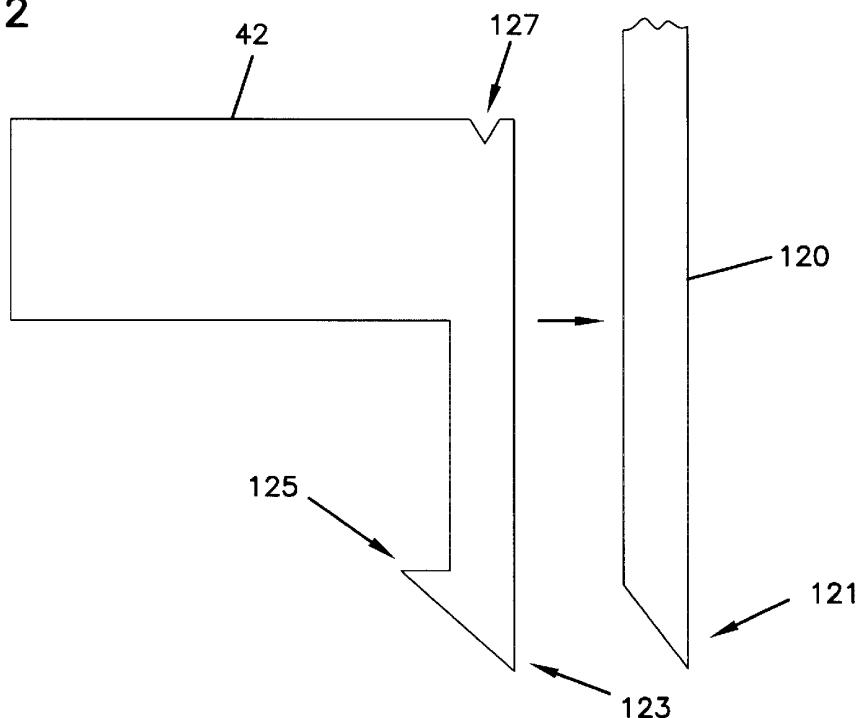


FIG. 13A

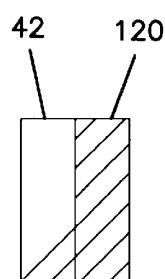


FIG. 13B

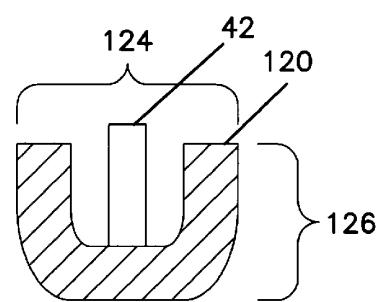


FIG. 13C

